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REVIEW OF GASTRO RETENTIVE DRUG DELIVERY SYSTEMS EFFECTIVE AGAINST H PYLORI

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Abstract:

Oral drug delivery still remains user friendly form, having the highest degree of patient compliance, and highly preferred route of drug administration. As such, drug for chronic condition are often administered orally for ease of long term use. The peroral dosage form cannot achieve prolongation of effective plasma concentration and effective bioavailability due to the changing environment in the GIT. This is because of various physiological problems like gastric emptying, motility, pH of the stomach etc. This can be overcome by developing suitable dosage form that could be retained in the stomach for prolong period. Drugs having narrow absorption window, stability problem and which need to act locally in stomach can be formulated as a floating drug delivery system. Such systems improve bioavailability, enhances absorption despite first pass effect, avoid the fluctuation in plasma drug concentration and maintain desirable level by continuous drug release. It also improves patient compliance by reducing dosing frequency and decrease wastage of drug. The multiple particulate unit dosage forms are more reliable and are freely distributed throughout GI tracts as compared to single unit formulation, which suffers "all or none concept.

Keywords: *Gastro Retentive, H Pylori, Stomach*

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INTRODUCTION:

The stomach has four main regions: the cardia, fundus, body and pyloric part. The cardiac surrounds the superior opening of the stomach. The rounded portion superior to and to the left of the cardia is the fundus. Inferior to the fundus is the large central portion of the stomach, the body. The pyloric part is divisible into three regions. The first region, the pyloric antrum, connects to the body of the stomach.The second region, the pyloric canal, leads to the third region, the pylorus, which in turn connects to the duodenum. When the stomach is empty, the mucosa lies in large folds, or rugae, that can be seen with the unaided eye. The pylorus communicates with the duodenum of the small intestine via a smooth muscle sphincter called the pyloric sphincter. The concave medial border of the stomach is lesser curvature; the convex lateral border is greater curvature

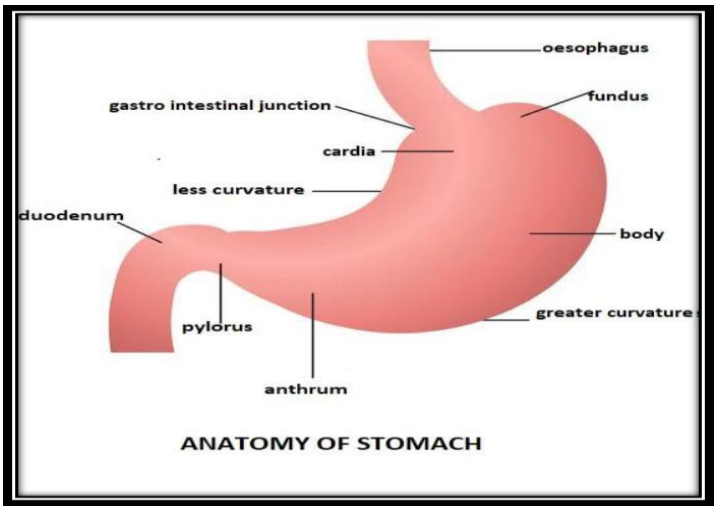

Fig.No 1- Anatomy of Stomach

Functions of Stomach:

The functions of the stomach include the following10

- Temporary storage allowing time for the digestive enzymes, pepsins, to act
- Chemical digestion –pepsins break proteins into polypeptides.
- Mechanical breakdown- the three smooth muscle layers enable the stomach to act as a churn, gastric juice has added and the contents are liquified to chime. Gastric motility and secretion has increased by parasympathetic nerve stimulation.
- Limits absorption- water, alcohol and some lipid soluble drugs.
- Non-specific defence against microbes- provided by hydrolytic acid in gastric juice. Vomiting may occur in response to ingestion of gastric irritants, e.g. microbes or chemicals.
- Preparation of iron for absorption- the acid environment of the stomach solubilises iron salts, essential for iron absorption in the small intestine.
- Production and secretion of intrinsic factor needed for absorption of vitamin B12 in the terminal ileum.
- Regulation of the passage of gastric contents into the duodenum. When the chyme is sufficiently acidified and liquefied, the pylorus forces small jets of gastric contents through the pyloric sphincter in the duodenum. The sphincter is normally closed, preventing, backflow of chime into the stomach.

Advantages of Grdds:

The advantages regarding gastro retentive drug delivery system includes

- It has been using in the treatment of peptic ulcer disease.
- Commonly used for drug having narrow therapeutic index. To minimize the dosing frequency.
- Improved bioavailability of drugs.
- Used for drugs which are normally unstable in intestinal fluids.
- Used to provide sustained delivery for the drugs used for maintaining maximum therapeutic drug concentration within the therapeutic withdraw.

Disadvantages of Grdds:

Although there are advantages, this also having disadvantages12,13. They are

- Drugs that are unstable in high acidic environment, very low solubility in acid environment causes irritation to gastric mucosa and cannot formulated as GRDDS.
- FDDS (Floating Drug Delivery Systems) require high level of fluid in stomach for floating and working more efficiently. So more water intake has needed with such dosage form.

Factors Affecting Grdds:

Density:

The density of the dosage form should be less than that of the gastric contents (1.004g/ml).

Size:

Dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form

Shape of the dosage form:

A diameter resided in the stomach for a longer period than other devices of similar size. The single or multiple unit formulation –multiple unit formulation show a greater predictable release profile and insignificant impairing of the performance due to failure of the units with different release profile or containing incompatible substances and permit larger margin of safety against dosage form failure compared with single unit dosage form

Fed or unfed state:

Under fasting conditions, the GI motility has characterized by periods of strong motor activity that occurs every 1.5-2 hrs. The MMC (Migrating Motor Complex) sweeps undigested material form the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer

Nature of meal:

Feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state, thus decreasing gastric emptying, rate and prolonging drug release.

Caloric content:

GRT can increased by 4-10 hours with a meal that is high in protein and fat.

Frequency the meal:

Feeding increase over 400 min when successive meals given are compared with the single meal due to low frequency of MMC

Gender:

Mean ambulatory GRT in male (3,4hrs) is less compared with the age and race matched female counterparts (4,6hrs) regardless of height, weight and body surface

Age:

People with age more than 70 have a significant longer GRT.

Concomitant drug administration:

Anti-cholinergic like atropine and propantheline, opiates like codeine can prolong GRT.

Approaches for Gastro Retentive Drug Delivery System:

There are various approaches for formulating the gastro retentive drug delivery systems. Some of the methods has depicted.

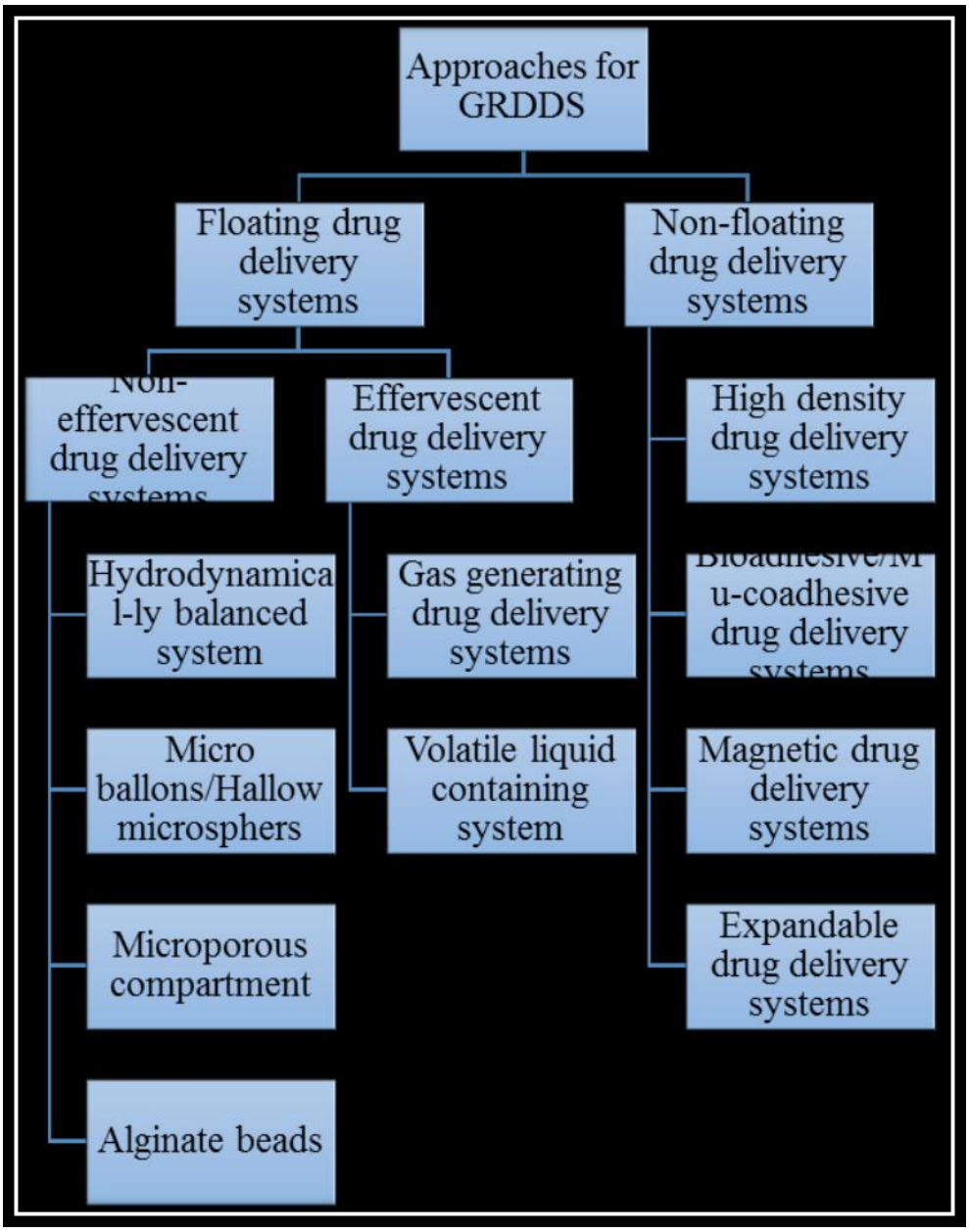

Fig.No 2: Approaches for GRDDS

Non-floating drug delivery systems:

a. High density (sinking) drug delivery system

The density of the formulation exceeds the density of the normal gastric content. The materials increase the density up to 1.5-2.4 gm/cm3. Depending on the density, the GI transit time of pellets can be extended from an average of 5.8-24 hours. But the effectiveness of this system in human beings was not observed and no formulation has been marketed

b. Bioadhesive or mucoadhesive drug delivery system

The gastric retention time has extended by adhering the bioadhesive system for gastric mucous membrane.The adherence of the delivery system to the gastric wall increases residence time thereby improving bioavailability. The chemicals used for the mucoadhesion purpose include polycarbophil, carbopol, lecithin, chitosan, carboxy methylcellulose, gliadin etc.,23. Novel adhesive material derived from fimbrae of bacteria or its synthetic analogues have also been tried for the attachment to the gut. However, the gastric mucoadhesive force does not tend to be strong enough to resist the propulsion force of the

stomach wall. The continuous production of mucus and dilution of the gastric content is another limitation for such type of system. Many investigators have tried out a synergestic approach between floating and bioadhesion system.

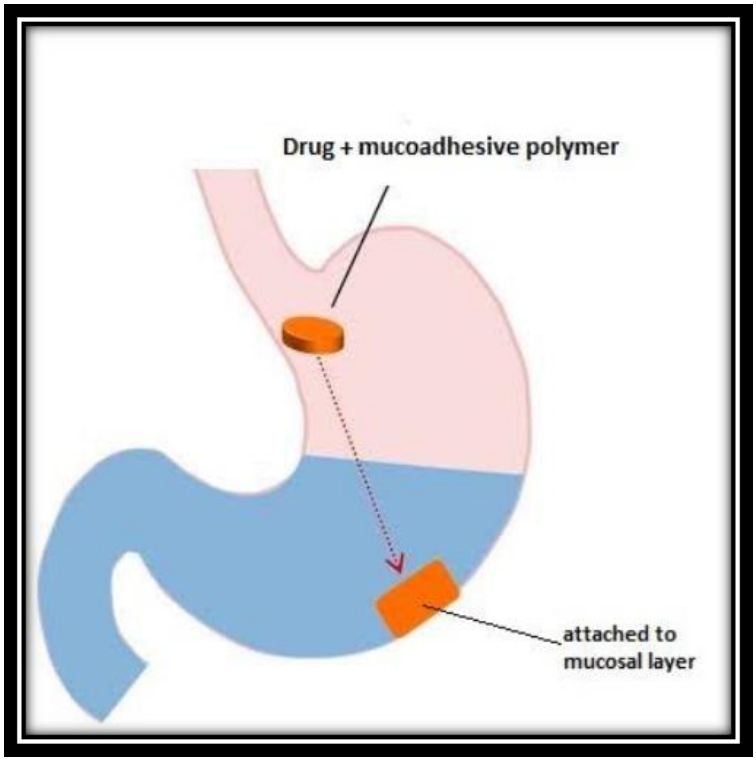

Fig.No 3: Mucoadhesive drug delivery system

c. Magnetic system:
In this system, the dosage form contains a small magnet and another magnet is placed on the abdomen over the position of the stomach. The external magnet should be placed with a degree of precision which may decrease the patient compliance.

d. Expandable System
These systems are capable of expanding and retain in the stomach for longer periods. These are usually formulated as a capsule containing dosage form folded and compact form. After being exposed to stomach environment, capsule shell disintegrates and dosage form expands preventing its exit through the stomach. By using a suitable polymer, sustained and controlled drug delivery can be achieved.

Floating Drug Delivery System
Effervescent System

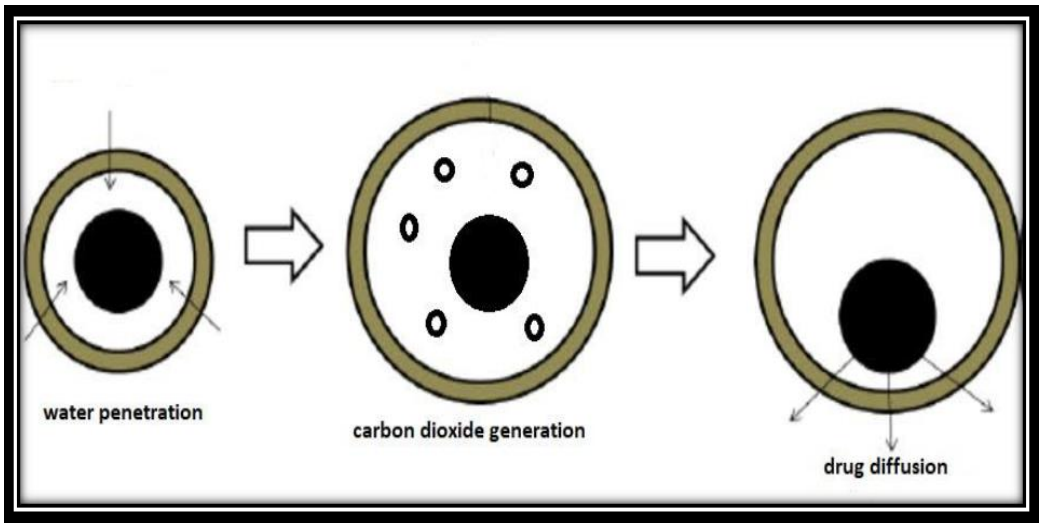

Fig.No 4: Effervescent drug delivery system

These systems was further classified into

i) Gas generating System:
The main mechanism is involved in this system is the production of CO2 gas due to reaction between sodium bicarbonate, citric acid and tartaric acid. The gas produced results in the reduction of density of the system, thereby making it float on the gastric fluids. Salts and citric/tartaric acid release CO2, which entrapped in the jellified hydrocolloid layer of the system which decrease its specific gravity and making it float over chime24. The system consist of a sustain release pill as seed surrounded by double layer. The inner layer is an effervescent layer containing sodium bi carbonate and tartaric acid. The outer layer is of a swellable membrane layer containing PVA shellac. (Fig. 4: Effervescent drug delivery system)

ii) Volatile liquid containing system
These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasify at body temperature to cause the inflation of the chamber in the stomach. These systems osmotically control floating system containing a hollow definable unit. These are two chambers in the system first contain the drug and the second chamber containing the volatile system.
These systems has again classified into following

- **Intra gastric floating gastrointestinal drug delivery system**

This system contains a floatation chamber which contains vacuum or an inert, harmless gas and a micro porous compartment enclosing drug reservoir.

- **Inflatable gastrointestinal drug delivery system**

These systems possess inflatable chamber containing liquid ether which gasifiers at body temperature to inflate the stomach. Inflatable chamber contains bio erodible polymer filament (e.g Copolymer of poly vinyl alcohol and poly ethylene) that gradually dissolves in gastric fluid and finally cause an inflatable chamber to release gas and collapse.

- **Intra-gastric osmotically controlled drug delivery system**

It is composed of osmotic pressure controlled drug delivery device and an inflatable floating capsule.in the stomach, inflatable capsule disintegrates and release the osmotically controlled drug delivery system which contains two components: drug reservoir compartment and osmotically active compartment. Superporous hydrogels are an excellent example, working on this approach. The dosage form swells significantly to several times of original volume upon contact with gastric fluid, the gastric contraction pushes the dosage form to the pylorus but due to the larger size of the dosage form , the contractions slips over the surface of the system, due to which the dosage form pushes back into the stomach.

b. Non-effervescent systems
Non-effervescent system can be further divided in to hydro dynamically balanced system, Microbaloons, alginate beads and microporous compartment

i. Hydrodynamically balanced system
It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach

contents .Drug Delivery Systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release slowly at a desired rate from the system. After the release of the drug, the residual system is emptified from the stomach. The results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations.

ii. Micro balloons

Micro balloons (Hollow microsphere) are in the strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometres. Micro balloons loaded with drug in their outer polymer shell are prepared by a novel methods such as solvent evaporation to create a hollow inner core. the drug and an enteric acrylic polymer mixture are dissolved in ethanol /dichloromethane solution and it is

poured into an agitated solution of Poly Vinyl Alcohol (PVA) that as thermally controlled at 40^0c. After the formation of stable emulsion, the organic solvent is evaporated from the emulsion by increasing the temperature under pressure or by continuous stirring. The gas phase is generated in the droplet of dispersed polymer by the evaporation of dichloromethane and thus formed the hollow internal cavity in the microsphere of the polymer with drugs.

iii. Microporous compartment

In this system, drug reservoir is encapsulated inside a microporous compartment having pores along its top and bottom walls. The floatation chamber containing entrapped air causes the delivery system to float over the gastric fluid enters through the aperture ,dissolves the drug and carries the dissolved drug in the stomach and proximal part of the small intestine for absorption.

iv. Alginate beads

Freeze dried calcium alginates have been used to develop multi unit floating dosage forms26. By dropping sodium alginate solution into aqueous solution of calcium chloride spherical beads of about 2.5 mm diameter can be prepared. These beads are separated and air dried. This results in the formation of aporous system which remains buoyant in the stomach.

1.7 Helicobacter pylori:

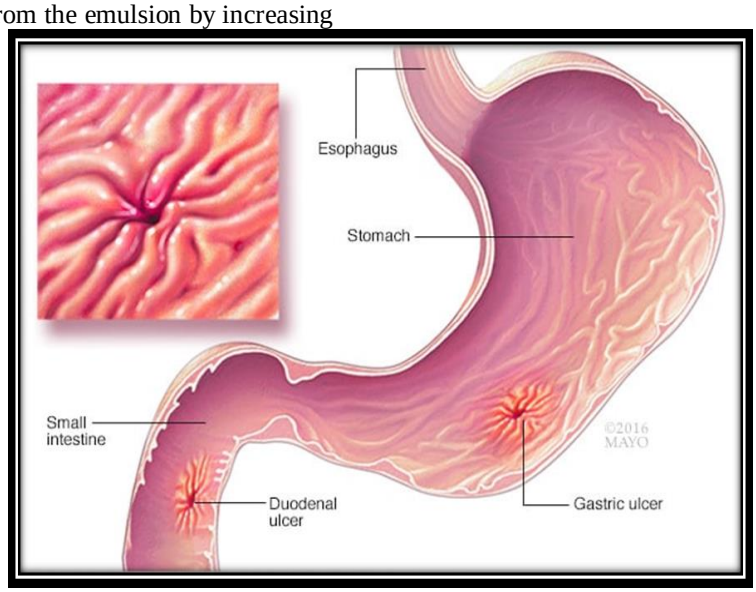

Fig.No 5: H. Pylori Infection site in stomach

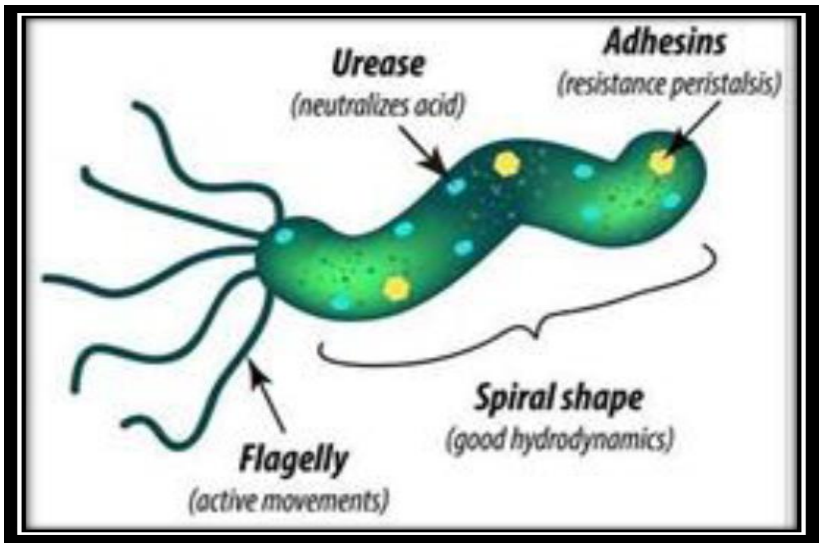

Fig.No 6: H. Pylori.

Helicobacter pylori, previously known as Campylobacter pylori, is a gram-negative, microaerophilic, spiral (helical) bacterium usually found in the stomach. Its helical shape (from which the genus name, helicobacter, derives) is thought to have evolved in order to penetrate the mucoid lining of the stomach and thereby establish infection. The bacterium was first identified in 1982 by the Australian doctors Barry Marshall and Robin Warren. H. pylori has been associated with cancer of the mucosa-associated lymphoid tissue in the stomach, esophagus, colon, rectum, or tissues around the eye (termed extranodal marginal zone B-cell lymphoma of the cited organ), and of lymphoid tissue in the stomach (termed diffuse large B-cell lymphoma).

H. pylori infection usually has no symptoms but sometimes causes gastritis (stomach inflammation) or ulcers of the stomach or first part of the small intestine. The infection is also associated with the development of certain cancers Many investigators have suggested that H. pylori causes or prevents a wide range of other diseases, but many of these relationships remain controversial.

Some studies suggest that H. pylori plays an important role in the natural stomach ecology, e.g. by influencing the type of bacteria that colonize the gastrointestinal tract.Other studies suggest that non-pathogenic strains of H. pylori may beneficially normalize stomach acid secretion, and regulate appetite.

In 2015, it was estimated that over 50% of the world's population had H. pylori in their upper gastrointestinal tracts with this infection (or colonization) being more common in developing countries. In recent decades, however, the prevalence of H. pylori colonization of the gastrointestinal tract has declined in many countries.

Signs and symptoms:

Up to 90% of people infected with H. pylori never experience symptoms or complications.[22] However, individuals infected with H. pylori have a 10% to 20% lifetime risk of developing peptic ulcers.Acute infection may appear as an acute gastritis with abdominal pain (stomach ache) or nausea Where this develops into chronic gastritis, the symptoms, if present, are often those of non-ulcer dyspepsia: Stomach pains, nausea, bloating, belching, and sometimes vomiting. Pain typically occurs when the stomach is empty, between meals, and in the early morning hours, but it can also occur at other times. Less common ulcer symptoms include nausea, vomiting, and loss of appetite.

Bleeding in the stomach can also occur as evidenced by the passage of black stools; prolonged bleeding may cause anemia leading to weakness and fatigue. If bleeding is heavy, hematemesis, hematochezia, or melena may occur. Inflammation of the pyloric antrum, which connects the stomach to the duodenum, is more likely to lead to duodenal ulcers, while inflammation of the corpus (i.e. body of the stomach) is more likely to lead to gastric ulcers. Individuals infected with H. pylori may also develop colorectal or gastric polyps, i.e. non-cancerous growths of tissue projecting from the mucous membranes of these organs. Usually, these polyps are asymptomatic but gastric polyps may be the cause of dyspepsia, heartburn, bleeding from the upper gastrointestinal

tract, and, rarely, gastric outlet obstruction while colorectal polyps may be the cause of rectal bleeding, anemia, constipation, diarrhea, weight loss, and abdominal pain.

Individuals with chronic H. pylori infection have an increased risk of acquiring a cancer that is directly related to this infection These cancers are stomach adenocarcinoma, less commonly diffuse large B-cell lymphoma of the stomach, or extranodal marginal zone B-cell lymphomas of the stomach or, more rarely, of the colon, rectum, esophagus, or ocular adenexa (i.e. orbit, conjunctiva, and/or eyelids). The signs, symptoms, pathophysiology, and diagnoses of these cancers are given in the cited linkages.

Morphology:
Helicobacter pylori is a helix-shaped (classified as a curved rod, not spirochaete) Gram-negative bacterium about 3 μm long with a diameter of about 0.5 μm. H. pylori can be demonstrated in tissue by Gram stain, Giemsa stain, haematoxylin–eosin stain, Warthin–Starry silver stain, acridine orange stain, and phase-contrast microscopy. It is capable of forming biofilms and can convert from spiral to a possibly viable but nonculturable coccoid form.

Helicobacter pylori has four to six flagella at the same location; all gastric and enterohepatic Helicobacter species are highly motile owing to flagella.The characteristic sheathed flagellar filaments of Helicobacter are composed of two copolymerized flagellins, FlaA and FlaB.

Physiology:
Helicobacter pylori is microaerophilic – that is, it requires oxygen, but at lower concentration than in the atmosphere. It contains a hydrogenase that can produce energy by oxidizing molecular hydrogen (H2) made by intestinal bacteria.It produces oxidase, catalase, and urease.

H. pylori possesses five major outer membrane protein families.The largest family includes known and putative adhesins. The other four families are porins, iron transporters, flagellum-associated proteins, and proteins of unknown function. Like other typical Gram-negative bacteria, the outer membrane of H. pylori consists of phospholipids and lipopolysaccharide (LPS). The O antigen of LPS may be fucosylated and mimic Lewis blood group antigens found on the gastric epithelium. The outer membrane also contains cholesterol glucosides, which are present in few other bacteria.

Genome:

Helicobacter pylori consists of a large diversity of strains, and hundreds of genomes have been completely sequenced the genome of the strain "26695" consists of about 1.7 million base pairs, with some 1,576 genes. The pan-genome, that is a combined set of 30 sequenced strains, encodes 2,239 protein families (orthologous groups, OGs). Among them, 1,248 OGs are conserved in all the 30 strains, and represent the universal core. The remaining 991 OGs correspond to the accessory genome in which 277 OGs are unique (i.e., OGs present in only one strain).

Genes involved in virulence and pathogenesis
Study of the H. pylori genome is centered on attempts to understand pathogenesis, the ability of this organism to cause disease. About 29% of the loci have a colonization defect when mutated. Two of sequenced strains have an around 40 kb-long Cag pathogenicity island (a common gene sequence believed responsible for pathogenesis) that contains over 40 genes. This pathogenicity island is usually absent from H. pylori strains isolated from humans who are carriers of H. pylori, but remain asymptomatic.

The cagA gene codes for one of the major H. pylori virulence proteins. Bacterial strains with the cagA gene are associated with an ability to cause ulcers. The cagA gene codes for a relatively long (1186-amino acid) protein. The cag pathogenicity island (PAI) has about 30 genes, part of which code for a complex type IV secretion system. The low GC-content of the cag PAI relative to the rest of the Helicobacter genome suggests the island was acquired by horizontal transfer from another bacterial species. The serine protease HtrA also plays a major role in the pathogenesis of H. pylori. The HtrA protein enables the bacterium to transmigrate across the host cells' epithelium, and is also needed for the translocation of CagA.

The vacA (Q48245) gene codes for another major H. pylori virulence protein. There are four main subtypes of vacA: s1/m1, s1/m2, s2/m1, and s2/m2. s1/m1 and s1/m2 subtypes are known to cause increased risk of gastric cancer.[55] This has been linked to the ability for toxigenic vacA to promote the generation of intracellular reservoirs of H. pylori via disruption of calcium channel TRPML1.

Proteome:
The proteins of H. pylori have been systematically analyzed by multiple studies. As a consequence, more than 70% of its proteome have been detected by mass spectrometry and other biochemical methods. In fact,

about 50% of the proteome have been quantified, that is, we know how many copies of each protein are present in a typical cell.Furthermore, the interactome of H. pylori has been systematically studied and more than 3000 protein-protein interactions have been identified. The latter provide information of how proteins interact with each other, e.g. in stable protein complexes or in more dynamic, transient interactions. This in turn helps researchers to find out what the function of uncharacterized proteins is, e.g. when an uncharacterized protein interacts with several proteins of the ribosome (that is, it is likely also involved in ribosome function). Nevertheless, about a third of all ~1,500 proteins in H. pylori remain uncharacterized and their function is largely unknown

Pathophysiology:

Adaptation to the stomach:

To avoid the acidic environment of the interior of the stomach (lumen), H. pylori uses its flagella to burrow into the mucus lining of the stomach to reach the epithelial cells underneath, where it is less acidic. H. pylori is able to sense the pH gradient in the mucus and move towards the less acidic region (chemotaxis). This also keeps the bacteria from being swept away into the lumen with the bacteria's mucus environment, which is constantly moving from its site of creation at the epithelium to its dissolution at the lumen interface.

H. pylori is found in the mucus, on the inner surface of the epithelium, and occasionally inside the epithelial cells themselves. It adheres to the epithelial cells by producing adhesins, which bind to lipids and carbohydrates in the epithelial cell membrane. One such adhesin, BabA, binds to the Lewis b antigen displayed on the surface of stomach epithelial cells.H. pylori adherence via BabA is acid sensitive and can be fully reversed by decreased pH. It has been proposed that BabA's acid responsiveness enables adherence while also allowing an effective escape from unfavorable environment at pH that is harmful to the organism.Another such adhesin, SabA, binds to increased levels of sialyl-Lewis X (sLeX) antigen expressed on gastric mucosa.

In addition to using chemotaxis to avoid areas of low pH, H. pylori also neutralizes the acid in its environment by producing large amounts of urease, which breaks down the urea present in the stomach to carbon dioxide and ammonia. These react with the strong acids in the environment to produce a neutralized area around H. pylori. Urease knockout mutants are incapable of colonization. In fact, urease expression is not only required for establishing initial colonization but also for maintaining chronic infection.

Adaptation of H. pylori to high acidity of stomach:

As mentioned above, H. pylori produce large amounts of urease to produce ammonia as one of its adaptation methods to overcome stomach acidity. Helicobacter pylori arginase, a bimetallic enzyme binuclear Mn2-metalloenzyme arginase, crucial for pathogenesis of the bacterium in human stomach, a member of the ureohydrolase family, catalyzes the conversion of L-arginine to L-ornithine and urea, where ornithine is further converted into polyamines, which are essential for various critical metabolic processes.

This provides acid resistance and is thus important for colonization of the bacterium in the gastric epithelial cells. Arginase of H. pylori also plays a role in evasion of the pathogen from the host immune system mainly by various proposed mechanisms, arginase competes with host-inducible nitric oxide (NO) synthase for the common substrate L-arginine, and thus reduces the synthesis of NO, an important component of innate immunity and an effective antimicrobial agent that is able to kill the invading pathogens directly.

Alterations in the availability of L-arginine and its metabolism into polyamines contribute significantly to the dysregulation of the host immune response to H. pylori infection.

Inflammation, gastritis and ulcer:

Helicobacter pylori harm the stomach and duodenal linings by several mechanisms. The ammonia produced to regulate pH is toxic to epithelial cells, as are biochemicals produced by H. pylori such as proteases, vacuolating cytotoxin A (VacA) (this damages epithelial cells, disrupts tight junctions and causes apoptosis), and certain phospholipases. Cytotoxin associated gene CagA can also cause inflammation and is potentially a carcinogen.

Colonization of the stomach by H. pylori can result in chronic gastritis, an inflammation of the stomach lining, at the site of infection. Helicobacter cysteine-rich proteins (Hcp), particularly HcpA (hp0211), are known to trigger an immune response, causing inflammation. H. pylori has been shown to increase the levels of COX2 in H. pylori positive gastritis. Chronic gastritis is likely to underlie H. pylori-related diseases.

Ulcers in the stomach and duodenum result when the consequences of inflammation allow stomach acid and the digestive enzyme pepsin to overwhelm the mechanisms that protect the stomach and duodenal mucous membranes. The location of colonization of

H. pylori, which affects the location of the ulcer, depends on the acidity of the stomach. In people producing large amounts of acid, H. pylori colonizes near the pyloric antrum (exit to the duodenum) to avoid the acid-secreting parietal cells at the fundus (near the entrance to the stomach). G-cells express relatively high levels of PD-L1 that protects these cells from H. pylori-induced immune destruction. In people producing normal or reduced amounts of acid, H. pylori can also colonize the rest of the stomach.

The inflammatory response caused by bacteria colonizing near the pyloric antrum induces G cells in the antrum to secrete the hormone gastrin, which travels through the bloodstream to parietal cells in the fundus. Gastrin stimulates the parietal cells to secrete more acid into the stomach lumen, and over time increases the number of parietal cells, as well.[76] The increased acid load damages the duodenum, which may eventually result in ulcers forming in the duodenum.

When H. pylori colonizes other areas of the stomach, the inflammatory response can result in atrophy of the stomach lining and eventually ulcers in the stomach. This also may increase the risk of stomach cancer.

Cag pathogenicity island:

The pathogenicity of H. pylori may be increased by genes of the cag pathogenicity island; about 50–70% of H. pylori strains in Western countries carry it. Western people infected with strains carrying the cag PAI have a stronger inflammatory response in the stomach and are at a greater risk of developing peptic ulcers or stomach cancer than those infected with strains lacking the island. Following attachment of H. pylori to stomach epithelial cells, the type IV secretion system expressed by the cag PAI "injects" the inflammation-inducing agent, peptidoglycan, from their own cell walls into the epithelial cells. The injected peptidoglycan is recognized by the cytoplasmic pattern recognition receptor (immune sensor) Nod1, which then stimulates expression of cytokines that promote inflammation.

The type-IV secretion apparatus also injects the cag PAI-encoded protein CagA into the stomach's epithelial cells, where it disrupts the cytoskeleton, adherence to adjacent cells, intracellular signaling, cell polarity, and other cellular activities. Once inside the cell, the CagA protein is phosphorylated on tyrosine residues by a host cell membrane-associated tyrosine kinase (TK). CagA then allosterically activates protein tyrosine phosphatase/protooncogene Shp2. Pathogenic strains of H. pylori have been shown to activate the epidermal growth factor receptor (EGFR), a membrane protein with a TK domain. Activation of the EGFR by H. pylori is associated with altered signal transduction and gene expression in host epithelial cells that may contribute to pathogenesis. A C-terminal region of the CagA protein (amino acids 873–1002) has also been suggested to be able to regulate host cell gene transcription, independent of protein tyrosine phosphorylation. A great deal of diversity exists between strains of H. pylori, and the strain that infects a person can predict the outcome.

Survival of Helicobacter pylori:

The pathogenesis of H. pylori depends on its ability to survive in the harsh gastric environment characterized by acidity, peristalsis, and attack by phagocytes accompanied by release of reactive oxygen species. In particular, H. pylori elicits an oxidative stress response during host colonization. This oxidative stress response induces potentially lethal and mutagenic oxidative DNA adducts in the H. pylori genome.

Vulnerability to oxidative stress and oxidative DNA damage occurs commonly in many studied bacterial pathogens, including Neisseria gonorrhoeae, Hemophilus influenzae, Streptococcus pneumoniae, S. mutans, and H. pylori For each of these pathogens, surviving the DNA damage induced by oxidative stress appears supported by transformation-mediated recombinational repair. Thus, transformation and recombinational repair appear to contribute to successful infection.

Transformation (the transfer of DNA from one bacterial cell to another through the intervening medium) appears to be part of an adaptation for DNA repair. H. pylori are naturally competent for transformation. While many organisms are competent only under certain environmental conditions, such as starvation, H. pylori is competent throughout logarithmic growth.[103] All organisms encode genetic programs for response to stressful conditions including those that cause DNA damage. In H. pylori, homologous recombination is required for repairing DNA double-strand breaks (DSBs). The AddAB helicase-nuclease complex resects DSBs and loads RecA onto single-strand DNA (ssDNA), which then mediates strand exchange, leading to homologous recombination and repair. The requirement of RecA plus AddAB for efficient gastric colonization suggests, in the stomach, H. pylori is either exposed to double-strand DNA damage that must be repaired or requires some other recombination-mediated event. In particular, natural transformation is increased by DNA damage in H. pylori, and a connection exists

between the DNA damage response and DNA uptake in H. pylori, suggesting natural competence contributes to persistence of H. pylori in its human host and explains the retention of competence in most clinical isolates.

RuvC protein is essential to the process of recombinational repair, since it resolves intermediates in this process termed Holliday junctions. H. pylori mutants that are defective in RuvC have increased sensitivity to DNA-damaging agents and to oxidative stress, exhibit reduced survival within macrophages, and are unable to establish successful infection in a mouse model. Similarly, RecN protein plays an important role in DSB repair in H. pylori. An H. pylori recN mutant displays an attenuated ability to colonize mouse stomachs, highlighting the importance of recombinational DNA repair in survival of H. pylori within its host.

Diagnosis:
H. pylori colonized on the surface of regenerative epithelium (Warthin-Starry silver stain)

Colonization with H. pylori is not a disease in itself, but a condition associated with a number of disorders of the upper gastrointestinal tract Testing is recommended if peptic ulcer disease or low-grade gastric MALT lymphoma (MALToma) is present, after endoscopic resection of early gastric cancer, for first-degree relatives with gastric cancer, and in certain cases of dyspepsia. Several methods of testing exist, including invasive and noninvasive testing methods.

Noninvasive tests for H. pylori infection may be suitable and include blood antibody tests, stool antigen tests, or the carbon urea breath test (in which the patient drinks 14C – or 13C-labelled urea, which the bacterium metabolizes, producing labelled carbon dioxide that can be detected in the breath). It is not known for sure which non-invasive test is more accurate for diagnosing a H. pylori infection but indirect comparison puts urea breath test as a higher accuracy than others.

An endoscopic biopsy is an invasive means to test for H. pylori infection. Low-level infections can be missed by biopsy, so multiple samples are recommended. The most accurate method for detecting H. pylori infection is with a histological examination from two sites after endoscopic biopsy, combined with either a rapid urease test or microbial culture.

Transmission:

Helicobacter pylori is contagious, although the exact route of transmission is not known. Person-to-person transmission by either the oral–oral (kissing, mouth feeding) or fecal–oral route is most likely. Consistent with these transmission routes, the bacteria have been isolated from feces, saliva, and dental plaque of some infected people. Findings suggest H. pylori is more easily transmitted by gastric mucus than saliva.[8] Transmission occurs mainly within families in developed nations, yet can also be acquired from the community in developing countries. H. pylori may also be transmitted orally by means of fecal matter through the ingestion of waste-tainted water, so a hygienic environment could help decrease the risk of H. pylori infection.

Prevention:
Due to H. pylori's role as a major cause of certain diseases (particularly cancers) and its consistently increasing antibiotic resistance, there is a clear need for new therapeutic strategies to prevent or remove the bacterium from colonizing humans.Much work has been done on developing viable vaccines aimed at providing an alternative strategy to control H. pylori infection and related diseases. Researchers are studying different adjuvants, antigens, and routes of immunization to ascertain the most appropriate system of immune protection; however, most of the research only recently moved from animal to human trials. An economic evaluation of the use of a potential H. pylori vaccine in babies found its introduction could, at least in the Netherlands, prove cost-effective for the prevention of peptic ulcer and stomach adenocarcinoma. A similar approach has also been studied for the United States. Notwithstanding this proof-of-concept (i.e. vaccination protects children from acquisition of infection with H. pylori), as of late 2019 there have been no advanced vaccine candidates and only one vaccine in a Phase I clinical trial. Furthermore, development of a vaccine against H. pylori has not been a current priority of major pharmaceutical companies.

Many investigations have attempted to prevent the development of Helicobacter pylori-related diseases by eradicating the bacterium during the early stages of its infestation using antibiotic-based drug regimens. Studies find that such treatments, when effectively eradicating H. pylori from the stomach, reduce the inflammation and some of the histopathological abnormalities associated with the infestation. However studies disagree on the ability of these treatments to alleviate the more serious histopathological abnormalities in H. pylori infections, e.g. gastric atrophy and metaplasia, both of which are precursors to gastric adenocarcinoma There

is similar disagreement on the ability of antibiotic-based regiments to prevent gastric adenocarcinoma. A meta-analysis (i.e. a statistical analysis that combines the results of multiple randomized controlled trials) published in 2014 found that these regimens did not appear to prevent development of this adenocarcinoma. However, two subsequent prospective cohort studies conducted on high-risk individuals in China and Taiwan found that eradication of the bacterium produced a significant decrease in the number of individuals developing the disease. These results agreed with a retrospective cohort study done in Japan and published in 2016as well as a meta-analysis, also published in 2016, of 24 studies conducted on individuals with varying levels of risk for developing the disease. These more recent studies suggest that the eradication of H. pylori infection reduces the incidence of H. pylori-related gastric adenocarcinoma in individuals at all levels of baseline risk. Further studies will be required to clarify this issue. In all events, studies agree that antibiotic-based regimens effectively reduce the occurrence of metachronous H. pylori-associated gastric adenocarcinoma. (Metachronous cancers are cancers that reoccur 6 months or later after resection of the original cancer.) It is suggested that antibiotic-based drug regimens be used after resecting H. pylori-associated gastric adenocarcinoma in order to reduce its metachronus reoccurrence.

Treatment:

Gastritis:

Superficial gastritis, either acute or chronic, is the most common manifestation of H. pylori infection. The signs and symptoms of this gastritis have been found to remit spontaneously in many individuals without resorting to Helicobacter pylori eradication protocols. The H. pylori bacterial infection persists after remission in these cases. Various antibiotic plus proton pump inhibitor drug regimens are used to eradicate the bacterium and thereby successfully treat the disorder[119] with triple-drug therapy consisting of clarithromycin, amoxicillin, and a proton-pump inhibitor given for 14–21 days often being considered first line treatment.

Peptic ulcers

Once H. pylori is detected in a person with a peptic ulcer, the normal procedure is to eradicate it and allow the ulcer to heal. The standard first-line therapy is a one-week "triple therapy" consisting of proton-pump inhibitors such as omeprazole and the antibiotics clarithromycin and amoxicillin. (The actions of proton pump inhibitors against H. pylori may reflect their direct bacteriostatic effect due to inhibition of the bacterium's P-type ATPase and/or urease. Variations of the triple therapy have been developed over the years, such as using a different proton pump inhibitor, as with pantoprazole or rabeprazole, or replacing amoxicillin with metronidazole for people who are allergic to penicillin. In areas with higher rates of clarithromycin resistance, other options are recommended. Such a therapy has revolutionized the treatment of peptic ulcers and has made a cure to the disease possible. Previously, the only option was symptom control using antacids, H2-antagonists or proton pump inhibitors alone.

Antibiotic-resistant disease

An increasing number of infected individuals are found to harbor antibiotic-resistant bacteria. This results in initial treatment failure and requires additional rounds of antibiotic therapy or alternative strategies, such as a quadruple therapy, which adds a bismuth colloid, such as bismuth subsalicylate. In patients with any previous macrolide exposure or who are allergic to penicillin, a quadruple therapy that consisting of a proton pump inhibitor, bismuth, tetracycline, and a nitroimidazole for 10–14 days is a recommended first-line treatment option. For the treatment of clarithromycin-resistant strains of H. pylori, the use of levofloxacin as part of the therapy has been suggested.

Ingesting lactic acid bacteria exerts a suppressive effect on H. pylori infection in both animals and humans, and supplementing with Lactobacillus- and Bifidobacterium-containing yogurt improved the rates of eradication of H. pylori in humans. Symbiotic butyrate-producing bacteria which are normally present in the intestine are sometimes used as probiotics to help suppress H. pylori infections as an adjunct to antibiotic therapy. Butyrate itself is an antimicrobial which destroys the cell envelope of H. pylori by inducing regulatory T cell expression (specifically, FOXP3) and synthesis of an antimicrobial peptide called LL-37, which arises through its action as a histone deacetylase inhibitor.

The substance sulforaphane, which occurs in broccoli and cauliflower, has been proposed as a treatment. Periodontal therapy or scaling and root planing has also been suggested as an additional treatment.

Epidemiology:

At least half the world's population is infected by the bacterium, making it the most widespread infection in the world.Actual infection rates vary from nation to nation; the developing world has much higher infection rates than the developed one (notably Western Europe, North America, Australasia), where rates are estimated to be around 25%.

The age when someone acquires this bacterium seems to influence the pathologic outcome of the infection. People infected at an early age are likely to develop more intense inflammation that may be followed by atrophic gastritis with a higher subsequent risk of gastric ulcer, gastric cancer, or both. Acquisition at an older age brings different gastric changes more likely to lead to duodenal ulcer. Infections are usually acquired in early childhood in all countries. However, the infection rate of children in developing nations is higher than in industrialized nations, probably due to poor sanitary conditions, perhaps combined with lower antibiotics usage for unrelated pathologies. In developed nations, it is currently uncommon to find infected children, but the percentage of infected people increases with age, with about 50% infected for those over the age of 60 compared with around 10% between 18 and 30 years. The higher prevalence among the elderly reflects higher infection rates in the past when the individuals were children rather than more recent infection at a later age of the individual. In the United States, prevalence appears higher in African-American and Hispanic populations, most likely due to socioeconomic factors. The lower rate of infection in the West is largely attributed to higher hygiene standards and widespread use of antibiotics. Despite high rates of infection in certain areas of the world, the overall frequency of H. pylori infection is declining. However, antibiotic resistance is appearing in H. pylori; many metronidazole- and clarithromycin-resistant strains are found in most parts of the world.

DRUG PROFILE:

Name: Vonoprazan
Molecular formula: C17H16FN3O2S
Molecular weight: Average: 345.39 g·mol−1
Description: Vonoprazan is used in form of the fumarate for the treatment of gastroduodenal ulcer (including some drug-induced peptic ulcers) and reflux esophagitis, and can be combined with antibiotics for the eradication of Helicobacter pylori Vonoprazan is a potassium-competitive acid blocker (PCAB) that inhibits H+, K+-ATPase-mediated gastric acid secretion. PCABs represent an alternative to proton-pump inhibitors for the treatment of acid-related disorders. Unlike proton-pump inhibitors, PCABs are not affected by CYP2C19 genetic polymorphisms and do not require acid-resistant formulations.1 Furthermore, vonoprazan is 350-times more potent than the proton-pump inhibitor lansoprazole, thanks to its ability to accumulate in the gastric corpus mucosa, specifically in the parietal cellsIn May 2022, the FDA approved the use of vonoprazan in a co-packaged product containing amoxicillin and clarithromycin for the treatment of H. pylori infection.5 Studies have shown that the concomitant use of vonoprazan, amoxicillin, and clarithromycin leads to an H. pylori eradication rate of approximately 90%.3

Structural formula:

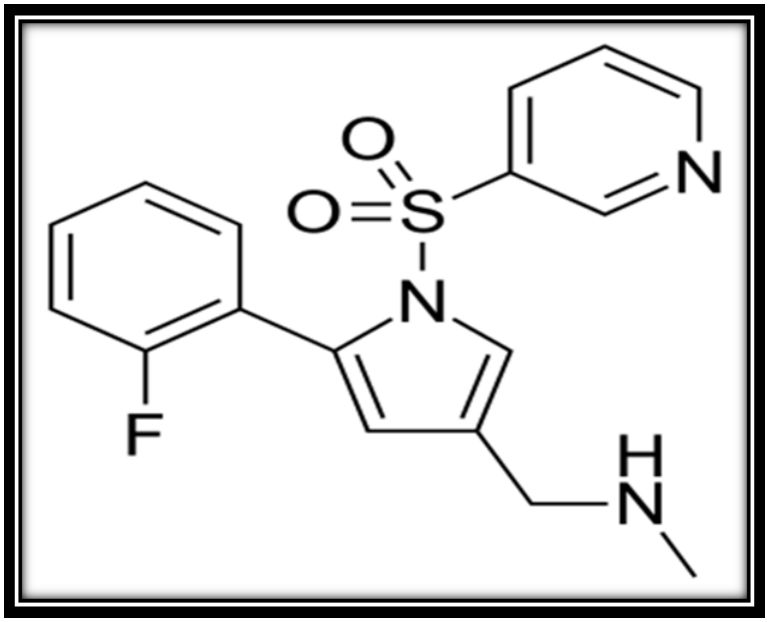

Fig.No.7 : Structure of Vonoprazan

Pharmacodynamics:
The use of vonoprazan leads to an increase in intragastric pH. The inhibitory effect of vonoprazan on acid secretion increases with repeated daily dosing. Although the antisecretory effect of vonoprazan decreases after drug discontinuation, intragastric pH remains elevated for 24 to 48 hours. Vonoprazan does not have a clinically significant effect on QT prolongation. Compared to other potassium-competitive acid blockers (PCABs), vonoprazan has a higher point-positive charge (pKa of 9.06). This allows vonoprazan to accumulate at higher concentrations in the canalicular space of the gastric parietal cells, where it binds H+, K+-ATPase in a K+-competitive and reversible manner. Compared to other PCABs, such as SCH28080, or proton-pump inhibitors, such as lansoprazole, vonoprazan has a more potent H+, K+-ATPase inhibitory activity.1

Mechanism of action
Vonoprazan is a potassium-competitive acid blocker (PCAB) that inhibits the H+, K+-ATPase enzyme system in a potassium-competitive manner. Through this mechanism, vonoprazan suppresses basal and stimulated gastric acid secretion at the secretory surface of gastric parietal cells.Although both classes of drugs inhibit the H+, K+-ATPase, the mechanism of action of PCABs differs from that of proton-pump inhibitors (PPIs). PPIs form a covalent disulphide bond with a cysteine residue on the H+, K+-ATPase, which leads to the inactivation of the enzyme, while PCABs interfere with the binding of K+ to the H+, K+-ATPase.

SUMMARY AND CONCLUSION:

Development of an efficient gastro retentive dosage form for stomach specific drug delivery is an actual challenge. Thus, to produce the preferred gastro retention several methods have been used, out of which, the floating drug delivery system has emerged as the best promising method. These systems provide the benefit of better absorption of drugs that are absorbed from upper part of stomach. Local action of drug is increased as the system rests in stomach for longer time. This leads to less frequent dosing and enhanced efficiency of the treatment. Good stability and better drug release as compared to other conventional dosage forms make such system more reliable. Drug absorption in GIT is a highly variable procedure and prolonging GI retention of the dosage form prolongs the time of drug absorption. Floating drug delivery system promises to be a potential approach for gastric retention. Though there are number of complications to be worked out to achieve extended GI retention, many companies are focusing toward commercializing this method.

REFERENCES:

1. Hoogerwerf HA, Pasricha PJ. Pharmacotherapy of gastric acidity, peptic ulcers and gastroesophageal reflux disease; Goodman &Gilman‟s pharmacological basis of therapeutics Brunton LL, Lazo JS, Parker KL, editors. USA: McGraw- Hill Companies, Inc, 2006; 11: 967-981.
2. Abbreviated Drug Class Review: Proton Pump Inhibitors, VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Homepage on the internet, 2006; 05. Available from: http://www.pbm.va.gov/reviews/ppiabbreviated rev iew.pdf
3. Hogan J. Modified release coatings, Pharmaceutical Coating Technology, Graham Cole,editor. UK: Taylor & Francis Ltd, 1995; 428.
4. Tian L, Zhang Y; Tang X, Sustained-Release Pellets Prepared by Combination of Wax Matrices and Double-Layer Coatings for Extremely Water-Soluble Drugs, Drug Development and Industrial Pharmacy. June, 2008; 34(6): 569 – 576.
5. Tanberk, New galenic process for the omeprazole pellets‟, EP0519144.Claudio N,Influence of formulation and process parameter on pellets production by powder layering technique using aqueous solution‟, AAPSPharm Scitech, 2014; 1(2).
6. Sharma D, Sharma A. Gastroretentive drug delivey system- A mini review. Asian Pac.J. Health Sci, 2014; 1(2): 80-89.
7. Kumar S, Jamil F, Rajput M and Sharma S. Gastro Retentive drug delivery system: features and facts. International journal of research in pharmaceutical and biomedical sciences, 2012; 3(1): 125-135.
8. Mentis A, Lehours P, Megraud F. Epidemiology and Diagnosis of Helicobacter pylori infection. Helicobacter, 2015; 20(1): 1–7.
9. Chey WD, Wong BC, Practice Parameters Committee of the American College of G.American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol, 2007; 102: 1808–1825. pmid:17608775
10. Atkinson NS, Braden B. Helicobacter Pylori Infection: Diagnostic Strategies in Primary Diagnosis and After Therapy. Dig Dis Sci, 2016; 61: 19–24. pmid:26391269.
11. Chey WD, Leontiadis GI, Howden CW, Moss

SF. ACG Clinical Guideline: Treatment of elicobacter pylori Infection. Am J Gastroenterol, 2017; 112: 212.
12. Gisbert JP, Gonzalez L, Calvet X. Systematic review and meta-analysis: proton pump inhibitor vs. ranitidine bismuth citrate plus two antibiotics in Helicobacter pylori eradication. Helicobacter, 2005; 10: 157.
13. Chawla G, Gupta P, Koradia V and Bansal AK. Gastroretension: A means to address regional variability in intestinal drug absorption. Pharmaceutical Technology. 2003;27:50-68.
14. Garg Re and Gupta GD. Progress in controlled gastro retentive delivery systems. Topical Journal of Pharmaceutical Research. 2008;7(3):1055-1066.
15. Yadav M, Sharma P, Chaudhary V and Srivastava B. Gastro retentive drug delivery system: a promising approach. Indo American Journal of Pharmaceutical Research. 2016;6(4):5225-5235.
16. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC and Falson Fir. Gastro retentive dosage forms: Overview and special case of Helicobacter pylori. J Control Release. 2006;111(1-2):1 -18.
17. Patil JM, Hirlekar RS, Gide PS and Kadam VJ. Trends in floating drug delivery systems. Journal of Scientific and Industrial Research. 2006;65(1):11-21.
18. Fujimori J, Machida Y, Tanaka S and Nagai T. Effect of magnetically controlled gastric residence of sustained release tablets on bioavailability of acetaminophen. International Journal of Pharmaceutics. 1995;119: 47-55.
19. Klausner EA, Lavy E, Friedman M and Hoffmann A. Expandable gastroretentive dosage forms. Journal of Controlled drug Release. 2003;90:143-162.
20. Thapa P and Jeong S. effects of formulation and process variables on gastroretentive floating tablets with a high- dose soluble drug and experimental design approach. Pharmaceutics. 2018;10:1-25.